REMARKS

Upon entry of the amendment, claims 1, 9-17, 31, 32, 34, 51-53, 67-69 and 77-85 will be pending. Claims 1, 14, 51, and 80 are amended, and new claims 81-85 are added by the amendment. Claims 2-8, 18-30, 33, 35-50, 54-66 and 70-76 have been canceled. Support for the amended and the new claims can be found in the specification as filed. For example, support for amended claim 51 can be found at least at page 40, line 28, through page 41, line 6. Support for new claim 81 can be found at least at page 20, line 31, to page 21, line 2; page 47, lines 10-19; page 52, line 33, to page 63, line 34; and page 63, lines 22-26. Support for new claims 82-85 can be found at least at page 20, lines 13-15, and at page 27, lines 5-7.

The claim amendments and cancellations made herein are for the purpose of expediting prosecution of the instant application. Applicants do not acquiesce to the rejections made by the Office, and reserve the right to pursue the canceled subject matter in one or more continuing applications.

A Supplemental Information Disclosure Statement (IDS) is attached. The Examiner is respectfully requested to consider the references on the attached form PTO/SB/08a and indicate that he has done so be initialing and returning a copy of the form to Applicants.

Applicants acknowledge with appreciation the withdrawal of previous rejections under 35 U.S.C. § 112, first and second paragraph; 35 U.S.C. § 102(e); and 35 U.S.C. § 103(a).

35 U.S.C. § 112, Second Paragraph

Claims 1, 9-17, 31, 32, 34, 51-53, 67-69 and 77-80 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Claims 1, 15, and 80, and the corresponding dependent claims, were rejected for referring to a peptide sequence without identifying the peptide by amino acid sequence identifier. Applicants respectfully traverse the rejection.

PYY_{3-36} corresponds to amino acids 3-36 of peptide YY, as explicitly recited in claim 1. This naturally occurring peptide is known in the art to be a gut derived hormone that is released post prandially in proportion to the calories ingested. See, *e.g.*, the Specification at page 108, lines 31-32. The definition of PYY_{3-36} is clearly defined in the specification, such as at pages 20-21, which state that PYY includes the human full length polypeptide as set forth in SEQ ID NO:1, and species variations as set forth at SEQ ID NOs:5-12. PYY_{3-36} also encompasses the mutant variations described, *e.g.*, at page 63, lines 22-34. Further, PYY_{3-36} is an art recognized term and one of ordinary skill in the art would understand the meaning of the term[1].

MPEP 2173.02 states:

> In reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the Examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. § 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent.

MPEP 2173.02 further states:

> [d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of: (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

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[1] See, for example, Dumont *et al.*, "Characterization of a Selective Neuropeptide Y/peptide YY Y2 Receptor Radioligand" *Society for Neuroscience Abstracts* 19:726, 1993; Eberlein *et al.* "A New Molecular form of PYY: structural characterization of human PYY(3-36) and PYY(1-36)" *Peptides* 10:797-803, 1989; Grandt *et al.*, "Two Molecular Forms of Peptide YY (PYY) are abundant in Human Blood: Characterization of a Radioimmunoassay Recognizing PYY 1-36 and PYY 3-36" *Regulatory Peptides* 67:151-159, 1996; and Grandt *et al.*, "Characterization of Two Forms of Peptide YY, PYY(1-36) and PYY(3-36), in the Rabbit" *Regulatory Peptides* 51:815-820, 1994, all cited in the Information Disclosure Statement submitted October 11, 2005.

In view of the disclosures in the specification, the knowledge in the art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made, claims 1, 15, and 80 are definite and satisfy the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore respectfully request that the rejection be withdrawn.

Claim 14 was rejected because it is unclear how intracisternal is peripheral administration. Intracisternal has been deleted, thereby rendering the rejection moot.

Claim 51 was rejected because it is allegedly unclear if the dose is per kg or per 70 to 75 kg body weight. Claim 51 has been amended to specify that the dose is 10 nmoles, 20 nmoles, 30 nmoles or 40 nmoles per 70 to 75 kilograms body weight of the subject. The meaning of the claim as amended is believed to be clear, and withdrawal of the rejection is therefore respectfully requested.

In view of the amendments and the above remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Double Patenting

Claims 1, 11, 12, 14-17, 31, 32, 51-53, 67-69 and 77-80 were rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 7,456,432 ("the '432 patent"). Applicants respectfully traverse the rejection.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s), because the examined application claim is either anticipated by or would have been obvious over the cited references. See, *e.g., In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). See also MPEP 804(II)(B)(1)(a). The pending claims are not obvious in view of the claims (or the relevant sections of the specification) of the '432 patent.

The claims issued in the '432 patent are directed to methods of, *inter alia*, controlling calorie intake, or for treating obesity, by administering PYY_{3-36}. By contrast, the claims pending in the present application are directed to methods of controlling calorie intake, or for treating obesity, by administering PYY_{3-36} in combination with GLP-1. The inventors of the subject matter of the pending claims discovered surprisingly that the use of these compounds together worked synergistically to control weight gain. See, *e.g.*, Example 8, at pages 115-116 of the specification, which demonstrates that coadministration of GLP -1 and PYY_{3-36} in rats caused "a clear synergistic effect on the reduction of food intake." In these experiments, PYY_{3-36} was administered at a dose of 3 μg/kg, which is within the dose limitation of the claims.[2]

See also Example 9, at pages 116-117 of the specification, which demonstrates that in humans, intravenous infusion of GLP-1 and PYY_{3-36}, also had a synergistic effect on the reduction of food intake. Again, PYY_{3-36} was administered at a low dose (48 pmol/kg) . The synergy of the claimed combination at low dosage levels is significant for the present invention.

There is no teaching in the '432 patent to suggest a synergistic effect of a combination of PYY_{3-36} and GLP-1, and particularly not at the low dose range of PYY_{3-36} required by the claims. The pending claims are therefore not obvious in view of those issued in the '432 patent, and Applicants respectfully request reconsideration and withdrawal of the double patenting rejection.

35 U.S.C. § 112, First Paragraph (Enablement)

Claim 14 was rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for peripheral administration that is intravenous, which does not typically require a high dose, allegedly does not reasonably provide enablement for any species of peripheral administration including subcutaneous, oral, and

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[2] The molecular weight of PYY_{3-36} is 4049.5 g/mol. Thus, 3 μg/kg is equivalent to 51.9-55.5 nmol per 70-75 kg bodyweight: 3 μg/kg (g/1*10^6 μg)(mol/4049.5 g)(1*10^9 nmol/mol)= 0.74 nmol/kg = 51.9- 55.5 nmol per 70-75 kg bodyweight.

transdermal. The PTO stated that such routes of administration are not enabled because "they typically require a higher dose to provide an effective concentration of a peptide upon delivery." Office Action at page 5. The PTO further stated that:

> [t]he claims are rejected because of undue experimentation to practice the claimed method for the genus of any peripheral route of administration for the concentrations contemplated for the method claimed. The undue experimentation arises due to the degradation of peptide based on the differing routes of administration.

Id.

The PTO, however, did not provide any factual evidence why these routes of administration would not be appropriate or effective to administer PYY_{3-36} and GLP-1 at the dosage required by the claims. Applicants respectfully traverse the rejection.

There is nothing in the art to suggest that the routes of administration listed in claim 14 would not be effective to decrease caloric intake, food intake, or appetite in a human subject. That some experimentation may be required to determine the optimum dose does not render the claim unpatentable for lack of enablement. The fact that experimentation may be complex does not necessarily mean it is undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n, 1983). Also, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976); see also MPEP § 2164.01. In the present situation, undue experimentation would not be required to determine the dose within the required range of 5 to 100 nmoles per 70 to 75 kilogram bodyweight most appropriate for administration of the agent by a route recited in claim 14.

Applicants provided working examples of administration intraperitoneally (IP) and by intravenous (i.v.) infusion in Examples 8 and 9 at pages 115-117. Applicants demonstrated a synergistic effect of low dose GLP-1 and PYY_{3-36} in rats by intraperitoneal administration (Example 8), and in humans by intravenous injection (Example 9). The Examiner has provided no reason why one of skill in the art would not

be able to administer the combination by other routes of administration to achieve a similar effect.

It is notable that Example 8 showed a synergistic effect on the reduction of food intake when PYY_{3-36} and GLP-1 were co-administered. See the Specification at page 115, lines 27-28. It is logical to conclude therefore that PYY_{3-36} and GLP-1 can be administered at lesser amounts to achieve a therapeutic effect when they are administered together than when they are administered alone, because they were shown to act synergistically. The Examiner does not cite any evidence contrary to the teachings in Applicants' specification, or supportive of his conclusion that the claimed compositions would be ineffective by the claimed peripheral routes of administration.

Applicants also attach a Declaration under 37 CFR § 1.132 by Dr. James Tobin (hereafter, the "Declaration"), Vice President and Chief Scientific Officer in the Biocorrection Research Unit (BRU) at Pfizer (formerly Wyeth) (Cambridge, MA), who has extensive experience in molecular and biochemistry research. Dr. Tobin states in the Declaration that studies performed by himself and his collaborators showed that a peptide about the same size as PYY_{3-36} was efficacious in humans and rats following subcutaneous administration. The peptide, an oxyntomodulin ("OXM") analog, was administered to humans subcutaneously at dosages ranging from 200 to 800 μg flat dose (equivalent to 49.4 nmol to 197.6 nmol flat dose; and 2.7 to 10.7 μg/kg in a 75 kg human). The OXM analog was administered subcutaneously to rats at 4.3 μg/kg to 193 μg/kg (equivalent to 1.06 nmol/kg to 47.66 nmol/kg, which extrapolates to about 79.5 nmol to 3574.5 nmol per 75 kg human).

PYY_{3-36} is 33 amino acids in length and the OXM analog tested above is 37 amino acids in length. The proteins are therefore similar molecular weights. It is therefore reasonable to predict that PYY_{3-36} would be capable of having efficacy at similar dosages demonstrated by OXM following subcutaneous administration.

To satisfy the enablement requirement, the specification must provide sufficient information to enable one skilled in the art to make and use the claimed invention without undue or unreasonable experimentation. MPEP 2164.01. There are many factors to be considered when determining whether there is sufficient disclosure to satisfy the enablement requirement. The PTO stated that while the analysis and conclusion of a lack of enablement are based on these factors and the evidence as a whole, it is not necessary to discuss each factor in the enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims.

The PTO reviewed several factors relevant to the enablement analysis: (i) the nature of the invention, (ii) the level of predictability in the art, (iii) the quantity of experimentation, (iv) the state of the prior art, and (v) the level of one of ordinary skill in the art. These factors are addressed below.

(i) Nature of the invention. The PTO stated at page 6 of the Office Action that the instant claims are directed to a method for decreasing caloric intake, food intake or appetite in a human subject in need thereof comprising peripherally administering prior to a meal to said subject PYY_{3-36} from about 45 to 135 pmoles per kg body weight of the subject. Applicants agree that this is the dosage range relevant to claim 15. However, the amount of PYY_{3-36} covered by claim 1 (from which claim 14 depends) is 66.7 to 1429 pmol per kg body weight of the subject[3].

(ii) the level of predictability in the art, (iii) the quantity of experimentation, and *(iv) the state of the prior art.* The PTO stated at page 7 of the Office Action that the prior art has shown a large quantity of experimentation is often necessary to overcome the unpredictable development of peptide pharmaceuticals to decrease appetite in humans.

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[3] 5 to 100 nmol (1x10^-9 mol/nmol)(1x10^12 pmol/mol) = 5000 to 100,000 pmol;
5000 to 100,000 pmol per 70 to 75 kg body weight of subject = 66.7 to 1429 pmol per kg body weight of subject

Applicants disagree with this conclusory statement. The Examiner is respectfully requested to provide specific references that would lead one of skill in the art to doubt that administration of PYY by the claimed methods would not be effective to decrease caloric intake, food intake or appetite in a human subject, as described in the specification.

The PTO further referred to Applicants' remarks in the Response submitted September 9, 2008 (the September 9th response), that Pittner *et al.* showed unexpected weight increase upon administration of low doses of PYY. Applicants disagree that the results in Pittner *et al.* are relevant to support a finding that any of Applicants' claimed routes of administration are not enabled. The experimental conditions in Pittner *et al.* differ from the claim limitations in a number of ways. For example, Pittner *et al.* did not test a combination of GLP-1 and PYY_{3-36} as required by the pending claims. Pittner only showed results of different administrations of different concentrations of PYY_{3-36}. Thus, the results presented in Pittner *et al.* cannot be directly compared to those presented by Applicants, and Pittner's results do not contradict those presented in the specification.

(v) The level of skill in the art. The PTO stated that "the level of skill in the art is high, at least that of a doctoral scientist with several years of experience in the art." Applicants agree that the level of skill in the art is high, and that one of ordinary skill in the art would have an advanced degree in the biological sciences, such as a Masters, Ph.D., or M.D.

The PTO concluded that absent direction/guidance, one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims. "Absent factual data to the contrary, the amount and level of experimentation is undue." Office Action at page 8. Applicants disagree that the amount and level of experimentation is undue. Applicants provided ample guidance in the specification, including at page 23, lines 9-12; page 27, lines 5-15; and page 40, line 9 to page 41, line 2. Applicants also provided working examples demonstrating a synergistic effect of

GLP-1 and PYY_{3-36} when administered at the low dosages in rats and humans by different routes of administration (by IP and intravenous injection, respectively).

Further, the art of drug formulation and delivery is advanced and practiced by artisans having a high level of skill. A drug formulator would be able to prepare a suitable formulation for administration by essentially any route. As a product is developed, in most cases one particular mode of administration will be favored, perhaps due to it being the most amenable for the active ingredient being used, or for commercial and/or compliance reasons. But the foregoing does not detract from the fact that other routes of administration are almost always available. No evidence to the contrary has been provided by the Examiner. Therefore the presumption that the present specification provides an enabling disclosure has not been rebutted.

The science of drug delivery is extremely well developed. When presented with an active ingredient having a particular set of properties, a drug formulator would be able to make appropriate compositions for various routes of administration using what is generally known in the art.

In view of the guidance provided in the specification, and the common knowledge of those skilled in the art, any experimentation required to practice the full scope of claim 14 is within the standards typically practiced and is not undue.

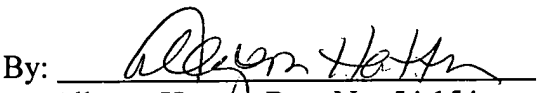
In view of the foregoing arguments, and the attached Declaration by Dr. Tobin, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

CONCLUSION

Applicants believe the claims are in condition for allowance, and notice to this effect is respectfully requested.

Please apply the $810 fee for the RCE, the fee of $2350 for the Petition for Extension of Time for five months, and any other necessary charges, or any credits, to Deposit Account No. 50-2762, referencing Attorney Docket No. W2023-7044US / AM103388.

Respectfully submitted,

By: 

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